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SYNTHESIS OF FUNCTIONALIZED PENICILLINS AND CEPHALOSPORINS BY PHOTO-INITIATED BROMINATION

A NOVEL ROUTE TO AMPICILLIN AND CEPHALEXIN FROM PENICILLIN G

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Abstract Photoinitiated bromination of the 1S-oxide ester **9**, available in two stages from penicillin G **6**, gave the diastereomeric bromides **10a** and **10b**. Both isomers have been utilized in further transformations to give the established antibiotics ampicillin **7** and cephalexin **8**.

In an earlier paper[1] we described the photo-initiated bromination of 2,2,2-trichloroethyl (1*S*, 6*R*, 7*R*)-7-phenylacetamido - 3 - methylceph - 3 - em - 4 - carboxylate, 1-oxide **1** to give the allylic bromides **2** and **3**. Also isolated were small amounts (< 5%) of the products **4** and **5** (as *ca* 1 : 1 mixtures of diastereomers) resulting from attack at the benzylic 2'-position of the phenylacetamido side chain. This suggested possible stereocontrolled routes to important 2'-substituted antibiotics such as ampicillin **7**[2] and cephalexin **8**[3,4] from readily available penicillin G **6** by procedures avoiding side chain removal and reacylation.

Photo-initiated bromination of the 1S-oxide ester **9** (available in two steps from penicillin G **6**[4]) with 1,3-dibromo-5,5-dimethylhydantoin (1.0 equiv.) in 1,2-dichloroethane at −12° gave a 76% yield of a 3:2 mixture of diastereomers **10a** and **10b** and some unreacted **9** (14%). More extensive chromatography of the product of a similar reaction using 1.2 equivalents of brominating agent gave 23% of the less polar isomer **10b**, shown by subsequent transformations (*vide infra*) to possess a 2'*S*-configuration, 10% of a mixture of isomers and 13% of the more polar isomer **10a**. The two isomers could be distinguished by their ^{1}H-NMR spectra in deuteriochloroform, in particular the sharp singlets attributed to the benzylic proton were quite distinct: δ5.41 for **10b** and 5.48 for **10a**. The diastereomeric excess (*de*)[5] of a particular isomer in a mixture could be estimated from its ^{1}H-NMR spectrum or by comparing its optical rotation with the $[\alpha]_D$ values obtained for the pure isomers.

Fractional crystallization of crude bromination products typically gave 30–35% of each diastereomer with *de* values in the range 60–95%. Any starting ester **9** crystallized mainly with the 2'*S*-isomer **10b**. Increased amounts of brominating agent led to reduced amounts of unchanged **9** but also to more decomposition and lower recoveries of the two isomers. This latter tendency could be lessened by adding some propylene oxide to the reaction mixture as an acid scavenger.

Equilibration of each diastereomer occurred with lithium bromide in N,N-dimethylacetamide (DMA). By utilizing lithium bromide and a small amount of DMA in chloroform–ethanol (1 : 1) it proved possible to convert, over a prolonged period and in good yield, the 2'*S*-isomer **10b** (*de* 60%) to crystalline 2'*R*-isomer **10a** (*de* > 95%). We were not able to effect the potentially more useful (*vide infra*) **10a** to **10b** transformation.

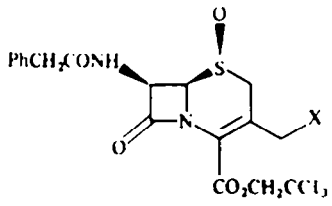
Displacement of the Br atom of **10a** and **10b** with azide ion [NaN_3 in N,N-dimethylformamide (DMF)] proceeded presumably with inversion of configuration for the bromide **10b**, $[\alpha]_D + 191°$, gave an azide **11a**, $[\alpha]_D + 54°$, and the bromide **10a**, $[\alpha]_D + 97°$, gave an azide **11b**, $[\alpha]_D + 248°$. The azide isomers could be distinguished by TLC but not by ^{1}H-NMR. It was not possible to interconvert either isomer, e.g. with base. Reaction of 2'*S*-bromide **10b**, *de* 70% obtained by fractional crystallization, under similar conditions gave crystalline 2'*R*-azide **11a** in 75% yield also with a *de* of 70%.

An attempt was made to use the unwanted 2'*R*-bromide diastereomer **10a** by adopting a double inversion sequence. Reaction of **10a**, *de* 60%, with an equivalent of potassium iodide in DMF followed by further reaction of the presumed predominantly 2'*S*-iodide intermediate with sodium azide (1.1 equiv) gave the 2'*R*-azide **11a** in 47% yield, *de* 54%.

Reduction of the 2'*R*-azide **11a** with stannous chloride in 2 N HCl–DMF gave the corresponding 2'*R*-amine **12a** in 66% yield. It was also possible to use optically impure **11a** in this step as any 2'*S*-amine **12b** formed did not co-crystallize with **12a**. For example, **11a** *de* 70% provided optically pure **12a** in 53% yield. Reaction of **12a** with trichloroethoxycarbonyl chloride in the presence of base gave the diprotected derivative **13** (86% yield, $[\alpha]_D + 96°$), identical with a sample of **13** ($[\alpha]_D + 95°$) prepared by a patented procedure[6] involving acylation of 6-aminopenicillanic acid with a mixed anhydride of D-α-phenyl-N-(2,2,2-trichloroethoxycarbonyl)glycine[4] followed by oxidation and esterification. The identity of the two samples confirmed the assigned stereochemistry at the 2'-position for compounds **10**–**12**.

Reduction of the sulphoxide **13** with potassium iodide–acetyl chloride[7] in DMF gave the corresponding sulphide in 81% yield. Removal of the ester function from **14** was achieved using Zn dust in aqueous acetic acid.[8] Purification by ion-exchange chromatography gave ampicillin **7** isolated as its crystalline naphthalene-2-sulphonate salt[9] in 40% yield.

A more direct route to ampicillin **7** was accomplished as follows: reduction of the azide sulphoxide **11a** with KI–AcCl in DMF gave the azide sulphide **15** in 79%



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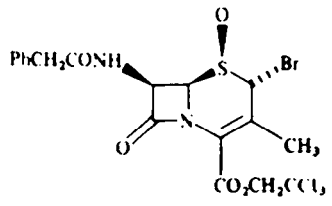
2 X = Br



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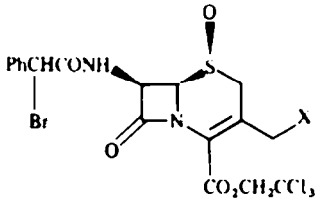
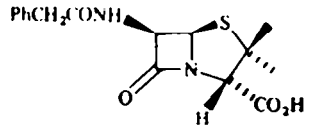
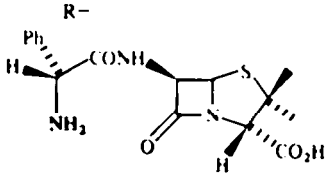


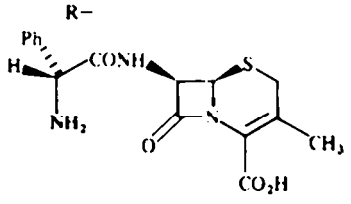
4 X = H
5 X = Br



6 Penicillin G



7 Ampicillin



8 Cephalexin

Scheme 1.

yield. Concomitant reduction of the azide function and de-esterification with Zn in aqueous acetic acid, using the procedure described previously for **14**, gave ampicillin **7** as its naphthalene-2-sulphonate salt in 56% yield. A disadvantage of this route was that it did not give the opportunity of removing any diasteromeric impurity as did the longer route proceeding *via* the amine **12a**.

Morin *et al.*[10] have described the acid-catalysed ring expansion of penicillin sulphoxide esters to 3-deacetoxycephalosporins. Rearrangement of the sulphoxide azide **11a** under modified conditions, *viz* using dichloromethanephosphonic acid mono-pyridinium salt as catalyst in refluxing dioxan and with azeotropic removal of the water formed,[11] gave the 3-methylcephem ester **16** in 86% yield. De-esterification and azide reduction of **16** with Zn in 90%-formic acid gave cephalexin **8** isolated at its isoelectric point in the presence of acetonitrile[4,12] (56% yield, corrected).

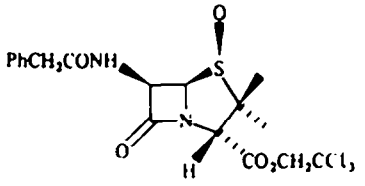
These transformations extend the utility of the photo-initiated bromination reaction for preparing functionalised β-lactam antibiotics[1,13,14] and also complement other procedures for obtaining ampicillin **7**[2,15] and cephalexin **8**.[3,4,16]

EXPERIMENTAL

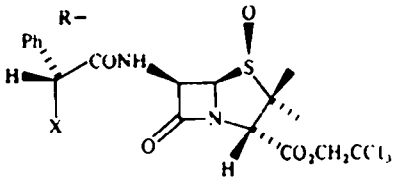
Unless stated otherwise the following procedures were adopted. M.ps were obtained on a Kofler Microblock and are uncorrected. Optical rotations were measured at 20–30° in $CHCl_3$ soln at 0.8–1.2% concentration. IR spectra were recorded in $CHBr_3$ soln on either a Perkin-Elmer model 21 or 521. ^{1}H-NMR spectra were obtained on 5–10% solns in $CDCl_3$ on a Varian A60 (60 MHz) or a Varian HA 100 (100 MHz). Coupling constants are quoted in Hz. The Hanovia Hg arc was placed in a Pyrex tube with its own cooling jacket, restricting the light to $\geq$ 300 nm. Solns were dried over $MgSO_4$ before evaporation *in vacuo* using a rotary evaporator.

Photo-initiated bromination of 2,2,2-trichloroethyl (1S,3S,5R,6R)-6-phenylacetamido-2,2-dimethylpenam-3-carboxylate,1-oxide **9**

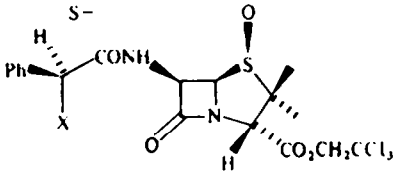
Isolation of the products by chromotography. A soln of **9**[4] (12.04 g, 25 mmol) in 1,2-dichloroethane (400 ml) was stirred at −15° under dry N_2 with DBDMH (4.3 g, 15 mmol) and



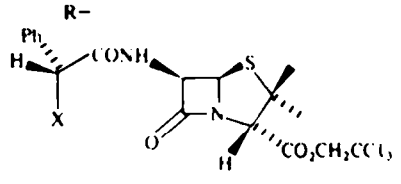
9



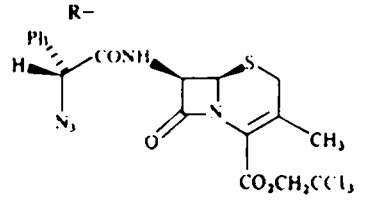
10a X = Br
11a X = N_3
12a X = NH_2
13 X = $NHCO_2CH_2CCl_3$



10b X = Br
11b X = N_3
12b X = NH_2



14 X = $NHCO_2CH_2CCl_3$
15 X = N_3



16

Scheme 2.

illuminated for 1.5 hr with a Hanovia 125W medium pressure Hg arc, the temp being kept at −20° throughout. The soln was washed with water (2 × 100 ml, the first containing some $Na_2S_2O_3$) dried and evaporated. The residual foam was chromatographed on Kieselgel G (400 g). Elution with benzene–EtOAc (6:1 followed by 2:1) gave first 2,2,2-*trichloroethyl*(1S,3S,5R,6R,2'S)-6-(2'-*bromo*-2'-*phenylacetamido*-2,2-*dimethylpenam*-3-*carboxylate*,1-*oxide* **10b** (3.30 g, 23.5%) which crystallized from hot EtOH (40 ml) as white prisms (2.27 g), m.p. 121–123°, $[\alpha]_D$ +191°, ν_{max} 3390 (NH), 1796 (azetidin-2-one), 1763 (CO_2R), 1676 and 1510 (CONH) and 1038 (S → O) cm^{-1}; δ1.30; 1.80 (s; Me_2), 4.67, 5.00 (AB-q, J12; CH_2CCl_3), 4.83 (s, C_3—H), 5.10 (d, J5; C_5—H), 5.41 (s; 2'S—H), 6.00 (dd, J5, 10; C_6—H), 7.3–7.6 (m; Ph), 8.10 (d, J10; NH) [Found: C, 38.6; H, 3.2; N, 5.0; S, 5.9; total halogen content 3.90 g atom/mol. $C_{18}H_{18}BrCl_3N_2O_5S$ (560.7) requires C, 38.6; H, 3.2; N, 5.0; S, 5.7; total halogen content 4.00 g atom/mol]; followed by a mixed fraction (1.42 g, 10.1%) and then by 2,2,2-*trichloroethyl*(1S,3S,5R,6R,2'R)-6-(2'-*bromo*-2'-*phenylacetamido*)-2,2-*dimethylpenam*-3-*carboxylate*, 1-*oxide* **10a** (1.76 g, 12.6%) which crystallized from hot EtOH (20 ml) as white prisms (1.28 g), m.p. 126–129°, $[\alpha]_D$ +97°, ν_{max} 3380 (NH), 1808 (azetidin-2-one), 1770 (CO_2R), 1682 and 1520 (CONH) and 1040 (S → O) cm^{-1}; δ1.32, 1.81 (s; Me_2), 4.68, 5.04 (AB-q, J12; CH_2CCl_3), 4.83 (s; C_3—H), 5.09 (d, J5; C_5—H), 5.48 (s; 2'*R*—H), 6.04 (dd, J5, 10; C_6—H), 7.3–7.6 (m; Ph), 8.20 (d, J10; NH) [Found C, 38.8; H, 3.2; N, 5.0; S, 5.7%; total halogen content 3.90 g atom/mol].

Isolation of the products by fractional crystallization. A soln of **9**[4] (24.06 g, 50 mmol) in 1,2-dichloroethane (800 ml) was stirred at −15° under dry N_2 with propylene oxide (20 ml) and DBDMH (12.55 g, 43.7 mmol) was irradiated as described above to give, after a similar work-up, a crude product which crystallized from hot EtOH (100 ml) to give a mixture of **10a** and **10b** (20.80 g, 74.2%), $[\alpha]_D$ +156°. A portion (10.0 g) in $CHCl_3$–EtOH (1:1, 140 ml) was seeded with pure **10a** and stored at −15° for 3 days. The crystals were collected, washed with cold EtOH (10 ml) to give **10a** (4.17 g, 31.0%), $[\alpha]_D$ +111° (*de*[5] 70%). The filtrate and washings were evaporated and the residue crystallized from EtOH (140 ml) to give **10b** (4.27 g, 31.7%), $[\alpha]_D$ +188° (*de*[5] 94%).

Conversion of **10b** *to* **10a** *by equilibration crystallization.* A soln of **10b** (1.0 g) and LiBr (1.0 g) in $CHCl_3$–EtOH (1:1, 40 ml) containing N,N-dimethylacetamide (0.5 ml) was cooled to 0° and seeded with **10a**. After 6 days the crystals were collected to give diastereomerically pure **10a** (700 mg), $[\alpha]_D$ +97.5°.

2,2,2-*Trichloroethyl*(1S,3S,5R,6R,2'R)-6-(2'-*azido*-2'-*phenylacetamido*)-2,2-*dimethylpenam*-3-*carboxylate*, 1-*oxide* **11a**

Preparation of optically pure diastereomer. A soln of optically pure **10b** (561 mg, 1 mmol) in DMF (10 ml) was stirred with NaN_3 (195 mg, 3 mmol) for 30 min then diluted with water (20 ml) and extracted with EtOAc (2 × 10 ml). The combined extracts were washed with water (10 ml) and NaCl aq (10 ml) then dried and evaporated to give a white foam (533 mg). This was purified by prep TLC on silica gel, eluting with benzene–EtOAc (6:1) to give a white foam (405 mg) which crystallized from EtOH (10 ml) to give **11a** as white crystals (303 mg, 58%), m.p. 100–101°, $[\alpha]_D$ +54°, ν_{max} 3380 (NH), 2130 (N_3), 1802 (azetidin-2-one), 1768 (CO_2R), 1694 and 1516 (CONH) and 1042 (S → O) cm^{-1}; δ1.31; 1.80 (s; Me_2), 4.64, 5.02 (AB-q, J12;

CH_2CCl_3), 4.81 (s; C_3—H), 5.07 (d, J5; C_5—H), 5.09 (s; 2'R—H), 6.02 (dd, J5, 10; C_6—H), 7.41 (s; Ph), 8.03 (d, J10; NH) [Found: C, 41.4; H, 3.5; N, 13.65; S, 6.3; Cl, 20.2. $C_{18}H_{18}Cl_3N_5O_5S$ (522.8) requires C, 41.4; H, 3.5; N, 13.5; S, 6.1; Cl, 20.3%].

Preparation by a fractional crystallization route. A soln of **10b** (*de* 70%) (3.36 g, 6 mmol) in DMF (60 ml) was stirred with NaN_3 (1.17 g, 18 mmol) for 30 min then worked up as above to give a white foam (3.25 g). This crystallized from EtOH (90 ml) over 2 days at −15° to afford **11a** as white crystals (2.37 g, 75%), m.p. 90–92°, $[\alpha]_D$ + 84° (*de* 70%).

Preparation by a double inversion procedure. A soln of **10a** (*de* 60%) 5.82 g, 10.4 mmol) in DMF (116 ml) was added over 30 min to a solution of KI (1.72 g, 10.4 mmol) in DMF (58 ml) while protecting the reaction from light. The resulting solution was stirred for 30 min then NaN_3 (742 mg, 11.4 mmol) was added. After a further 50 min the reaction was worked up as previously to give a pale yellow foam (4.89 g) which crystallized from hot EtOH (70 ml) to afford **11a** (2.57 g, 47%), $[\alpha]_D$ + 103° (*de* 54%).

2,2,2-*Trichloroethyl*(1S,3S,5R,6R,2'S)-6-(2'-*azido*-2'-*phenylacetamido*)-2,2-*dimethylpenam*-3-*carboxylate*, 1-*oxide* **11b**

A soln of optically pure **10a** (561 mg, 1 mmol) in DMF (10 ml) was treated with NaN_3 (195 mg, 3 mmol) as described above for the 2'S-isomer to give a white foam (550 mg). This was purified by prep TLC as previously to give a white foam (403 mg) which crystallized from aqueous EtOH (*ca* 10 ml) to give white prisms (183 mg, 35%), m.p. 78–80°, $[\alpha]_D$ + 266°, ν_{max} 3400 (NH), 2130 (N_3), 1802 (azetidin-2-one), 1768 (CO_2R), 1692 and 1512 (CONH) and 1040 (S → O) cm^{-1}; δ1.32 and 1.81 (s; Me_2), 4.67 and 5.03 (AB-q, J12; CH_2CCl_3), 4.82 (s, C_3—H), 5.04 (d, J5; C_5—H), 5.09 (s, 2'S-H), 6.00 (dd, J5, 10; C_6—H), 7.42 (s; Ph), 8.02 (d, J10; NH) [Found: C, 41.7; H, 3.5; N, 13.4; S, 6.2; Cl, 20.0. $C_{13}H_{18}Cl_3N_5O_5S$ (522.8) requires: C, 41.4; H, 3.5; N, 13.5; S, 6.1; Cl, 20.3%]. The liquors provided a further crop of similar material (84 mg, 16%), m.p. 72–79°, upon standing.

2,2,2-*Trichloroethyl*(1S,3S,5R,6R,2'R)-6-(2'-*amino*-2'-*phenylacetamido*)-2,2-*dimethylpenam*-3-*carboxylate*, 1-*oxide* **12a**

$SnCl_2$ dihydrate (113 mg, 0.5 mmol) then 2 N HCl (3 ml) were added to a stirred soln of **11a** (104 mg, 0.2 mmol) in DMF (7 ml). After 2 h the soln was diluted with 1N HCl (14 ml) and washed with EtOAc (2 × 7 ml). The aq portion was adjusted to pH 7 with satd $NaHCO_3$aq and extracted with EtOAc (2 × 10 ml). The combined extracts were washed with NaClaq (10 ml), dried and concentrated to *ca* 3 ml whereupon **12a** was deposited as white crystals (66 mg, 66%), m.p. 167–168°, $[\alpha]_D$ + 126°, ν_{max} 3400–3250 (NH_2 + CONH), 1790 (azetidin-2-one), 1760 (CO_2R), 1670, 1500 (CONH), and 1040 cm^{-1} (S → O), δ1.30, 1.78 (s; Me_2), 1.84 (s; NH_2), 4.55 (s, 2'R—H), 4.67, 5.02 (AB-q, J12; CH_2CCl_3), 4.80 (s; C_3—H), 5.05 (d, J5; C_5—H), 6.00 (dd, J5, 10; C_6—H), 7.36 (s; Ph), 8.56 (d, J10; NH) [Found: C, 43.2; H, 4.2; Cl, 20.65; N, 8.2; S, 6.2. $C_{18}H_{20}Cl_3N_5O_5S$ (496.8) requires C, 43.5; H, 4.05; Cl, 21.4; N, 8.5; S, 6.5%].

In similar fashion **11a** ($[\alpha]_D$ + 84°, *de* 70%) (523 mg, 1 mmol) was converted to **12a** (263 mg, 53%), $[\alpha]_D$ + 125°.

Using an identical procedure the 2'S-azide **11b** (208 mg, 0.4 mmol) was transformed to 2,2,2 - *trichloroethyl* (1S,3S,5R,6R,2'S) - 6 - (2' - *amino* - 2' - *phenylacetamido*) - 2,2 - *dimethylpenam* - 3 - *carboxylate*, 1-*oxide* **12b** as a white solid (113 mg, 57%), $[\alpha]_D$ + 212°, ν_{max} 3450–3200 (NH_2 + CONH), 1796 (azetidin-2-one), 1764 (CO_2R), 1680, 1500 (CONH) and 1040 (S → O) cm^{-1}; δ1.30, 1.81 (s; Me_2), 2.10 (s; NH_2), 4.61 (s; 2'S—H), 4.67, 5.01 (ABq, J12; CH_2CCl_3), 4.82 (s; C_3—H), 5.00 (d, J5; C_5—H), 5.98 (dd, J5, 10; C_6—H), 7.3–7.6 (m; Ph), 8.76 (d, J10; NH) [Found: C, 44.0; H, 4.0; Cl, 19.95; N, 8.2; S, 6.5. $C_{18}H_{20}Cl_3N_5O_5S$ (496.8) requires C, 43.5; H, 4.0; Cl, 20.4; N, 8.5; S, 6.5%].

2,2,2-*Trichloroethyl*(1S,3S,5R,6R,2'R)-6-(2'-*phenyl*-2'-[2,2,2-*trichloroethoxycarbonylamino*]*acetamido*)-2,2-*dimethylpenam*-3-*carboxylate*, 1-*oxide* **13**

2,2,2-Trichloroethylchloroformate (0.125 ml, 0.92 mmol) and NEt_3 (0.13 ml, 0.92 mmol) were added to a stirred soln of **12a** (418.5 mg, 0.84 mmol) in CH_2Cl_2 (6 ml). After 2 hr the soln was washed with 2 N HCl, satd $NaHCO_3$aq and water (6 ml each) then dried and evaporated to give a white foam (566 mg) which crystallized from ether–isopropanol (1:4) to give **13** as white needles (486 mg, 86%), m.p. 174–175° [lit[6] m.p. 185–186°], $[\alpha]_D$ + 95° [a sample of **13** prepared according to the literature procedure[6] had m.p. 172–173°, $[\alpha]_D$ + 95°], ν_{max} 3370 (NH), 1796 (azetidin-2-one), 1760 (CO_2R), 1730, 1506 ($NHCO_2R$), 1690, 1510 (CONH) and 1040 (S → O) cm^{-1}; δ1.24, 1.73 (s; Me_2), 4.65, 5.00 (AB-q, J12; C_3—$CO_2CH_2CCl_3$), 4.71 (s; $NHCO_2CH_2CCl_3$), 4.76 (s; C_3—H), 4.96 (d, J5; C_5—H), 5.30 (d, J6; 2'R—H), 6.02 (dd, J5, 10; C_6—H), 6.39 (d, J6; $NHCO_2R$), 7.40 (s; Ph); 7.55 (d, J10; CONH) [Found: C, 37.6; H, 3.4; Cl, 30.85; N, 6.1; S, 5.1. Calc for $C_{21}H_{21}Cl_6N_3O_7S$ (672.2) C, 37.5; H, 3.15; Cl, 31.6; N, 6.25; S, 4.8%].

2,2,2-*Trichloroethyl*(3S,5R,6R,2'R)-6-(2'-*phenyl*-2'-[2,2,2-*trichloroethoxycarbonylamino*]*acetamido*)-2,2-*dimethylpenam*-3-*carboxylate* **14**

KI (1.2 g) and AcCl (0.2 ml) were added to a stirred soln **13** (269 mg, 0.4 mmol) in DMF (4 ml) at 0°. The mixture was stirred at 5° for 1 hr then diluted with $Na_2S_2O_3$aq (8 ml) and extracted with EtOAc (2 × 4 ml). The combined extracts were successively washed with water, satd $NaHCO_3$aq and NaClaq (4 ml each) then dried and evaporated to a white foam which crystallized from petroleum ether (b.p. 60–80°) to give **14** as prisms (212 mg, 81%) solvated with DMF (0.5M), m.p. 79–83°, $[\alpha]_D$ + 70°, ν_{max} 3380 (NH), 1780 (azetidin-2-one), 1760 (CO_2R), 1730, 1500 ($NHCO_2R$), 1690 and 1510 (CONH) cm^{-1}; δ1.51, 1.56 (s; Me_2); 4.53 (s; C_3—H), 4.70 (s; $NHCO_2CH_2CCl_3$); 4.70 and 4.84 (AB-q, J12; C_3—$CO_2CH_2CCl_3$), 5.33 (d, J7, 2'R—H), 5.50 (d, J4; C_5—H), 5.66 (dd, J4, 9; C_6—H), 6.41 (d, J7; $NHCO_2R$), 6.75 (d, J9; CONH), 7.38 (s; Ph) with singlets at 2.88 and 2.95 for DMF (0.5 M) [Found: C, 39.7; H, 3.7; Cl, 30.6; N, 6.4; S, 4.9. $C_{21}H_{21}Cl_6N_3O_6S \cdot 0.5C_3H_7NO$ (692.8) requires: C, 39.0; H, 3.6; Cl, 30.7; N, 7.1; S, 4.6%].

2,2,2-*Trichloroethyl*(3S,5R,6R,2'R)-6-(2'-*azido*-2'-*phenylacetamido*)-2,2-*dimethylpenam*-3-*carboxylate* **15**

KI (1.0 g) and AcCl (0.5 ml) were added to a stirred soln **11a** (523 mg, 1 mmol) in DMF (10 ml) at 0°. The reaction was stirred for 1 hr at 5° then diluted with $Na_2S_2O_3$aq (20 ml) and extracted with EtOAc (2 × 10 ml). The combined extracts were successively washed with water, satd $NaHCO_3$aq and NaClaq (10 ml each) then dried and evaporated to give a foam (515 mg). This was purified by chromatography on Kieselgel G, eluting with benzene–EtOAc (12:1), to give **15** as a white foam (400 mg, 79%), $[\alpha]_D$ + 43°, ν_{max} 3400 (NH), 2130 (N_3), 1782 (azetidin-2-one), 1766 (CO_2R), 1692 and 1514 (CONH) cm^{-1}; δ1.60, 1.71 (s; Me_2), 4.59 (s; C_3—H), 4.72, 4.87 (AB-q, J12; CH_2CCl_3), 5.11 (s; 2'R—H), 5.55–5.80 (m; C_6—H and C_5—H), 7.16 (d, J8; NH), 7.42 (s; Ph) [Found: C, 43.2; H, 4.0; Cl, 20.2; N, 14.1; S, 6.4. $C_{18}H_{18}Cl_3N_5O_4S$ (506.8) requires C, 42.7; H, 3.6; Cl, 21.0; N, 13.8; S, 6.3%].

(3S,5R,6R,2'R)-6-(2'-*Amino*-2'-*phenylacetamido*)-2,2-*dimethylpenam*-3-*carboxylic acid* (*D-ampicillin*) **7**

From the diprotected derivative **14**. Zn dust (4.92 g) was added to a stirred soln of **14** (1.64 g, 2.5 mmol) in AcOH—H_2O (9:1, 25 ml) at 10°. The mixture was stirred for 5 min then filtered and the filter pad washed with AcOH—H_2O (9:1, 10 ml). The combined filtrates were passed through a column of Deacidite FF ion-exchange resin (Cl^- cycle, 15 ml) eluting with AcOH—H_2O (9:1, 75 ml). The eluate was freeze dried to give a white solid which was partitioned between 1N HCl (11 ml) and ether (50 ml). The aqueous portion was cooled to 0–5°

and treated with a soln of sodium naphthalene-2-sulphonate (520 mg, 2.26 mmol) in 1N HCl (10 ml) whilst maintaining the pH at 1.8 by adding 2 N NaOH. After 6 hr at 0–5° the white crystals were collected, washed with water (3 ml) and EtOAc (6 ml) and dried to give *ampicillin hydrogen naphthalene-2-sulphonate* (589 mg, 40%), $[\alpha]_D + 160°$ (pH 7 phosphate) having IR and ^{1}H-NMR spectra similar to those of material obtained[9] from authentic D-ampicillin Na salt [Found: C, 53.3; H, 5.1; N, 7.5; S, 10.9. Calc for $C_{26}H_{27}N_3O_5S_2 \cdot 5H_2O$ (584.65): C, 53.4; H, 5.2; N, 7.3; S, 11.1%].

From the azide ester **15**. A soln of **15** (*de* 90%) (1.27 g, 2.5 mmol) in AcOH—H_2O (9 : 1, 25 ml) at 10° was treated with Zn dust (3.70 g) essentially as described above for **14** to give *ampicillin hydrogen naphthalene-2-sulphonate* (812 mg, 56%). ^{1}H-NMR (DMSO-d_6) revealed impurity singlets at δ1.50 and 1.61 corresponding to some 2'*S*-isomer (*ca* 0.05 M).

2,2,2-*Trichloroethyl*(6R,7R,2'R)-7-(2'-*azido*-2'-*phenylacetamido*)-3-*methylceph*-3-*em*-4-*carboxylate* **16**

A soln of **11a** (1.70 g, 3.25 mmol) and dichloromethanephosphonic acid mono-pyridinium salt (100 mg, 0.41 mmol) in dioxan (50 ml) was heated at reflux for 10 hr. The condensed solvent passed through a bed of 4A molecular sieves before returning to the reaction vessel. The reaction soln was evaporated and the residue dissolved in ether (50 ml) and the soln re-evaporated to give a dark foam (2.04 g). This was chromatographed on Kieselgel G (50 g) using benzene–EtOAc (19 : 1) to give **16** as a white foam (1.41 g, 86%), $[\alpha]_D - 9.5°$, λ_{max} (EtOH) 260 nm (ε 5980); ν_{max} (nujol) 3330 (NH), 2110 (N_3), 1768 (azetidin-2-one), 1722 (CO_2R), 1680 and 1504 (CONH) cm^{-1}; δ2.20 (s; C_3—CH_3), 3.23 and 3.53 (AB-q, J18; C_2—H_2), 4.77 and 4.98 (AB-q, J12; CH_2CCl_3), 5.01 (d, J4; C_6—H), 5.10 (s; 2'R—H), 5.75 (dd, J4, 9; C_7—H), 7.25 (d, J9, NH); 7.3 7.5 (m; Ph) [Found: C, 42.7; H, 3.3; Cl, 20.1; N, 13.9; S, 6.3. $C_{18}H_{16}Cl_3N_5O_4S$ (504.8) requires: C, 42.85; H, 3.2; Cl, 21.0; N, 13.9; S, 6.3%].

(6R,7R,2'R)-7-(2'-*Amino*-2-*phenylacetamido*)-3-*methylceph*-3-*em*-4-*carboxylic acid* (*D-cephalexin*) **8**

A soln of **16** (1.10 g, 2.18 mmol) in formic acid (5 ml) was added to a stirred mixture of Zn (3 g) in formic acid (2 ml). An immediate evolution of a gas occurred. The mixture was stirred at 45° for 1.5 hr and filtered through a pad of Celite. The filtrate was passed through a column of Deacidite FF ion-exchange resin (Cl cycle; 30 ml) eluted with formic acid water (9 : 1, 150 ml). The eluate was evaporated to give a white foam (1.24 g) which was dissolved in water (3 ml)–formic acid (0.1 ml) and acetonitrile (10 ml). The pH was adjusted to 4.5 with triethylamine and the resulting slurry refrigerated for 30 min and filtered to give **8** solvated with acetonitrile (0.4 M) (444 mg, 56% correc.), $[\alpha]_D + 139°$ (*c* 0.67; H_2O); λ_{max} (H_2O) 260.5 nm (ε 7490), with IR and ^{1}H-NMR spectra similar to those obtained on authentic material.

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